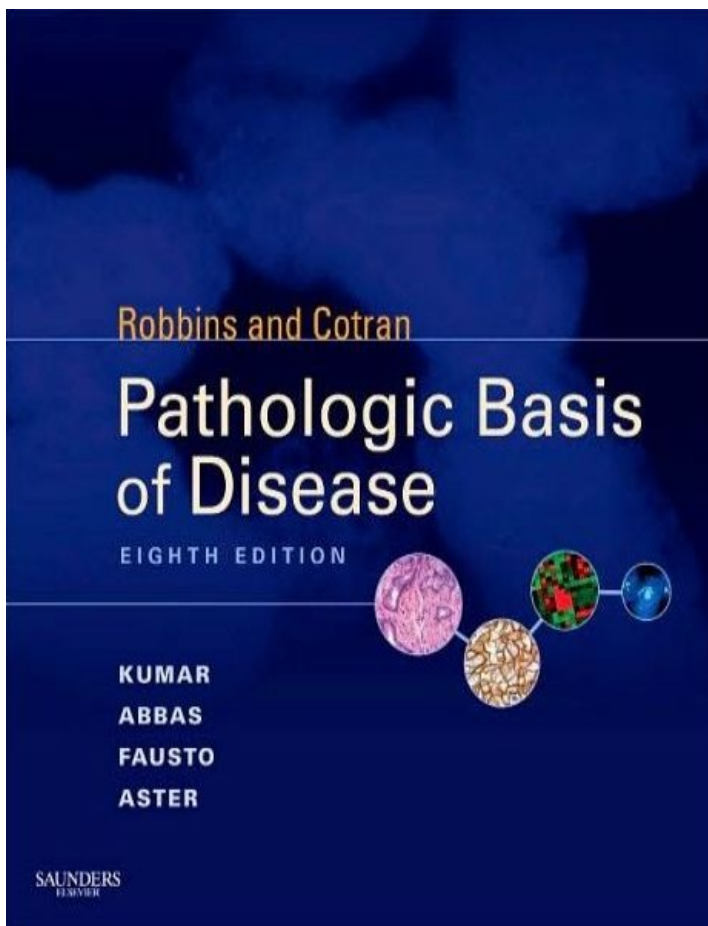


# **EXHIBIT JJ**



## Chapter 1 – Cellular Responses to Stress and Toxic Insults: Adaptation, Injury, and Death

### Introduction to Pathology

Pathology is the study (*logos*) of disease (*pathos*). More specifically, it is devoted to the study of the structural, biochemical, and functional changes in cells, tissues, and organs that underlie disease. By the use of molecular, microbiologic, immunologic, and morphologic techniques, pathology attempts to explain the whys and wherefores of the signs and symptoms manifested by patients while providing a rational basis for clinical care and therapy. It thus serves as the bridge between the basic sciences and clinical medicine, and is the scientific foundation for all of medicine.

Traditionally the study of pathology is divided into general pathology and systemic pathology. The former is concerned with the reactions of cells and tissues to abnormal stimuli and to inherited defects, which are the main causes of disease. The latter examines the alterations in specialized organs and tissues that are responsible for disorders that involve these organs. In this book we first cover the principles of general pathology and then proceed to specific disease processes as they affect particular organs or systems.

The four aspects of a disease process that form the core of pathology are its cause (*etiology*), the mechanisms of its development (*pathogenesis*), the biochemical and structural alterations induced in the cells and organs of the body (*molecular and morphologic changes*), and the functional consequences of these changes (*clinical manifestations*).

#### Etiology or Cause.

The concept that certain abnormal symptoms or diseases are “caused” is as ancient as recorded history. For the Arcadians (2500 BC), if someone became ill it was the patient's own fault (for having sinned) or the effects of outside agents, such as bad smells, cold, evil spirits, or gods. [1] We now recognize that there are two major classes of etiologic factors: genetic (e.g., inherited mutations and disease-associated gene variants, or polymorphisms) and acquired (e.g., infectious, nutritional, chemical, physical). The idea that one etiologic agent is the cause of one disease—developed from the study of infections and single-gene disorders—is not applicable to the majority of diseases. In fact, most of our common afflictions, such as atherosclerosis and cancer, are multifactorial and arise from the effects of various external triggers on a genetically susceptible individual. The relative contribution of inherited susceptibility and external influences varies in different diseases.

#### Pathogenesis.

Pathogenesis refers to the sequence of events in the response of cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease. The study of pathogenesis remains one of the main domains of pathology. Even when the initial cause is known (e.g., infection or mutation), it is many steps removed from the expression of the disease. For example, to understand cystic fibrosis is to know not only the defective gene and gene product, but also the biochemical and morphologic events leading to the formation of cysts and fibrosis in the lungs, pancreas, and other organs. Indeed, as we shall see throughout the book, the molecular revolution has already identified mutant genes underlying a great number of diseases, and the entire human genome has been mapped. Nevertheless, the functions of the encoded proteins and how mutations induce disease—the pathogenesis—are still often obscure. Technologic advances are making it increasingly feasible to link specific molecular abnormalities to disease manifestations and to use this knowledge to design new therapeutic approaches. For these reasons, the study of pathogenesis has never been more exciting scientifically or more relevant to medicine.

#### Molecular and Morphologic Changes.

Morphologic changes refer to the structural alterations in cells or tissues that are either characteristic of a disease or diagnostic of an etiologic process. The practice of diagnostic pathology is devoted to identifying the nature and progression of disease by studying morphologic changes in tissues and chemical alterations in patients. More recently the limitations of morphology for diagnosing diseases have become increasingly evident, and the field of diagnostic pathology has expanded to encompass molecular biologic and immunologic approaches for analyzing disease states. Nowhere is this more striking than in the study of tumors; breast cancers that look morphologically identical may have widely different courses, therapeutic responses, and prognosis. Molecular analysis by techniques such as DNA microarrays ( Chapter 5 ) has begun to reveal genetic differences that predict the behavior of the tumors as well as their responsiveness to different therapies. Increasingly, such techniques are being used to extend and even supplant traditional morphologic analyses.

#### Functional Derangements and Clinical Manifestations.

The end results of genetic, biochemical, and structural changes in cells and tissues are functional abnormalities, which lead to the clinical manifestations (symptoms and signs) of disease, as well as its progress (clinical course and outcome).

Virtually all forms of disease start with molecular or structural alterations in cells, a concept first put forth in the nineteenth century by Rudolf Virchow, known as the father of modern pathology. We therefore begin our consideration of pathology with the study of the causes, mechanisms, and morphologic and biochemical correlates of *cell injury*. Injury to cells and to extracellular matrix ultimately leads to *tissue and organ injury*, which determine the morphologic and clinical patterns of disease.